

Claims

We claim:

1. A crystal composition comprising a ternary complex of a compound, a protein, and a poly-nucleic acid wherein the protein is covalently linked to a phosphorous of the poly-nucleic acid.
2. A crystal composition of claim 1, wherein the compound is an inhibitor of a topoisomerase.
3. A crystal composition comprising a complex of a compound and topoisomerase covalently linked to a poly-nucleic acid substrate.
4. A crystal composition of claim 3 wherein the protein is a eukaryotic topoisomerase.
5. A crystal composition of claim 3, wherein the nucleic acid is DNA.
6. A crystal composition of claim 3, wherein the nucleic acid is duplex DNA.
7. A crystal composition comprising a complex of a compound and human topoisomerase I covalently linked to a duplex DNA substrate.
8. A crystal composition of claim 7, wherein the compound is an inhibitor of a topoisomerase.
9. The crystal composition of claim 7 wherein the crystal structure is crystal Form 7, Form 8, Form 9, Form 10, or Form 11.
10. A three-dimensional structure of a fully active form of human topoisomerase I in complex with duplex DNA (Form 7).
11. A three-dimensional structure of a compound contacting human topoisomerase I in covalent complex with duplex DNA.
12. The structure of claim 11 in which the compound is topotecan in the crystal Form9-TTC.
13. The structure of claim 11 in which the compound is AG260 in the crystal Form9-AG260.
14. The structure of claim 11 in which the compound is MJ-II-38 in the crystal Form 10.

15. The compound of claim 11 in which the compound is Hoechst-33342 in the crystal Form 11.
- 5 16. A method for identifying an agent which is an inhibitor of human topoisomerase I comprising:
 - (a) contacting the agent with topoisomerase I covalently linked to a duplex DNA substrate to form a complex;
 - 10 (b) growing a crystal of the complex and isolating the crystals of complex; and
 - (c) determining the three-dimensional crystal structure of the complex.
- 15 17. The method of claim 16 wherein novel compounds are tested to see if crystal structures are formed.
18. Novel compounds which complex and form a crystal structure in accordance with the method of claim 16.
- 20 19. A process for designing an inhibitor of a topoisomerase comprising:
 - (a) forming a crystalline composition of a compound and topoisomerase covalently bound to duplex DNA.
 - (b) solving the three-dimensional structure of the crystalline composition;
 - 25 (c) employing said three-dimensional structure to design or select a potential inhibitor;
 - (d) contacting said potential inhibitor with said topoisomerase in the presence of a substrate to determine the ability of said potential inhibitor to inhibit said topoisomerase.
- 30 20. A novel inhibitor of topoisomerase designed by the process of claim 19.
21. A inhibitor according to claim 20 which is an anti-cancer agent.
- 35 22. A inhibitor according to claim 20 which is an anti-microbial agent.
23. A inhibitor according to claim 20 which is an anti-viral agent.
- 40 24. The use of a topoisomerase and DNA to crystallize and determine the three-dimensional structure of a DNA binding agent.
25. A crystallant solution composed of: 8-13% (w/v) PEG-8000; 50-200 mM buffering agent at pH 6.3 to 6.6; 150-250 mM lithium sulfate, to

crystallize and solve the 3-D structures of complexes composed of human topoisomerase I, DNA and a compound.

26. The crystallant solution of Claim 25 wherein the buffering agent is MES-NaOH.
27. The crystallant solution of Claim 25 wherein the buffering agent is ADA-NaOH.